AMENDMENTS TO THE CLAIMS

Claim 1 (Currently Amended): A peptide that is a maturation product of the human Basic Proline-rich Lacrimal Protein (BPLP) or a peptide derivative of said maturation product, wherein the peptide or peptide derivative:

- exhibits an inhibitory property against a metallo-ectopeptidase~~, wherein said peptide~~
- ~~comprises 3 to~~ consists of at most 15 amino acids ~~and is obtained by cleavage of the BPLP protein precursor by furin, a PC convertase, or PACE 4, and said peptide derivative is obtained from said peptide by one to two amino acid substitutions and said peptide derivative retains the binding specificity and/or physiological activity of said peptide~~; and
- comprises the sequence X1-X2-Arg-Phe-Ser-Arg (SEQ ID NO: 6),

wherein:

- X1 represents H atom or a Tyr amino acid or a Cys amino acid,
- X2 represents Gln or Glp when Xl is H, or X2 represents Gln when Xl is Tyr or Cys,

and wherein said sequence X1-X2-Arg-Phe-Ser-Arg (SEQ ID NO: 6) is the C-terminal part of said peptide.

Claim 2 (Canceled):

Claim 3 (Original): The peptide of claim 1, wherein said metallo-ectopeptidase is NEP or APN.

Claim 4 (Canceled):

Claim 5 (Previously Presented): The peptide of claim 1, that consists of sequence X1-X2-Arg-Phe-Ser-Arg (SEQ ID NO: 6).

Claim 6 (Currently Amended): The peptide of ~~claim 4~~ claim 1, wherein the said peptide comprises the sequence QRFSR (SEQ ID NO: 3), YQRFSR (SEQ ID NO: 4), or CQRFSR (SEQ ID NO: 5).

Claim 7 (Previously Presented): The peptide of claim 6, which consists of sequence QRFSR (SEQ ID NO: 3).

Claim 8 (Previously Presented): The peptide of claim 6, which consists of sequence YQRFSR (SEQ ID NO: 4) .

Claim 9 (Previously Presented): The peptide of claim 6, which consists of sequence CQRFSR (SEQ ID NO: 5).

Claim 10 (Withdrawn): A nucleic acid that encodes a peptide of claim 1.

Claim 11 (Withdrawn): A vector for cloning and/or expression, which vector comprises a nucleic acid of claim 10.

Claim 12 (Withdrawn): A host cell comprising the nucleic acid of claim 10.

Claim 13 (Withdrawn): An antibody that specifically recognizes a peptide of claim 1.

Claim 14 (Withdrawn): An antibody that specifically recognizes the BPLP protein.

Claim 15 (Currently Amended): A pharmaceutical composition comprising a peptide according to claim 1 or a mimetic peptide thereof, in association with a pharmaceutically acceptable carrier, wherein said mimetic peptide retains the binding specificity and/or physiological activity of said peptide and is obtained through a structural modification of a peptide according to claim 1 selected from the group consisting of:

replacement of one or more of the amino acids with unnatural amino acids,

conformational restraints,

isosteric replacement,

cyclization,

replacement of one or more amide bonds with non-amide bonds,

replacement of one or more amino acid side chains with a different chemical moiety,

protection of one or more of the N-terminus, the C-terminus, or one or more side chains with a protecting group, double bond, cyclization, or sterospecificity,

protection of the NH_2 and COOH hydrophilic groups by esterification with lipophilic alcohols by amidation and/or acetylation,

addition of a carboxylalkyl or aromatic hydrophobic chain at the NH_2 terminus,

retroinversion of the CO-NH amide bonds,

methylation of the amide functions, and

substitution of L-amino acids with D-amino acids.

Claim 16 (Currently Amended): A pharmaceutical composition, comprising a polymer of a peptide according to claim 1, or a mimetic peptide thereof, in association with a pharmaceutically acceptable carrier, wherein said mimetic peptide retains the binding specificity and/or physiological activity of said peptide and is obtained through a structural modification of a peptide according to claim 1 selected from the group consisting of:

replacement of one or more of the amino acids with unnatural amino acids,

conformational restraints,

isosteric replacement,

cyclization,

replacement of one or more amide bonds with non-amide bonds,

replacement of one or more amino acid side chains with a different chemical moiety,

protection of one or more of the N-terminus, the C-terminus, or one or more side chains with a protecting group, double bond, cyclization, or sterospecificity,

protection of the NH_2 and COOH hydrophilic groups by esterification with lipophilic alcohols by amidation and/or acetylation,

addition of a carboxylalkyl or aromatic hydrophobic chain at the NH_2 terminus,

retroinversion of the CO-NH amide bonds,

methylation of the amide functions, and

substitution of L-amino acids with D-amino acids.

Claim 17 (Withdrawn): A pharmaceutical composition comprising a nucleic acid of claim 10.

Claim 18 (Withdrawn): A pharmaceutical composition comprising a nucleic acid coding for the BPLP protein or a vector expressing said nucleic acid.

Claim 19 (Withdrawn): A pharmaceutical composition comprising an antibody of claim 13.

Claims 20 - 21 (Canceled):

Claim 22 (Withdrawn): A method of preventing or treating a disease wherein a modulation of the activity of a membrane metallopeptidase is sought which comprises administering a patient in need thereof with a peptide according to claim 1 or a mimetic thereof, wherein said mimetic retains the binding specificity and/or physiological activity of said peptide and is obtained through a structural modification selected from the group consisting of:

replacement of one or more of the amino acids with unnatural amino acids,

conformational restraints,

isosteric replacement,

cyclization,

replacement of one or more amide bonds with non-amide bonds,

replacement of one or more amino acid side chains with a different chemical moiety,

protection of one or more of the N-terminus, the C-terminus, or one or more side chains with a protecting group, double bond, cyclization, or sterospecificity,

protection of the NH_2 and COOH hydrophilic groups by esterification with lipophilic alcohols by amidation and/or acetylation,

addition of a carboxylalkyl or aromatic hydrophobic chain at the NH_2 terminus,

retroinversion of the CO-NH amide bonds,

methylation of the amide functions, and

substitution of L-amino acids with D-amino acids.

Claim 23 (Withdrawn): The use of claim 22, wherein the metallopeptidase is a membrane-zinc metallopeptidase.

Claim 24 (Withdrawn): The use of claim 23, wherein the metallopeptidase is NEP or APN.

Claim 25 (Withdrawn): A method of preventing or treating pain which comprises administering a patient in need thereof with a peptide according to claim 1, or a mimetic thereof, wherein said mimetic retains the binding specificity and/or physiological activity of said peptide and is obtained through a structural modification selected from the group consisting of:

replacement of one or more of the amino acids with unnatural amino acids,

conformational restraints,

isosteric replacement,

cyclization,

replacement of one or more amide bonds with non-amide bonds,

replacement of one or more amino acid side chains with a different chemical moiety,

protection of one or more of the N-terminus, the C-terminus, or one or more side chains with a protecting group, double bond, cyclization, or sterospecificity,

protection of the NH_2 and COOH hydrophilic groups by esterification with lipophilic alcohols by amidation and/or acetylation,

addition of a carboxylalkyl or aromatic hydrophobic chain at the NH_2 terminus,

retroinversion of the CO-NH amide bonds,

methylation of the amide functions, and

substitution of L-amino acids with D-amino acids.

Claim 26 (Withdrawn): The use of claim 25, wherein the pain is chronic, acute, visceral inflammatory or neuropathic pain.

Claim 27 (Withdrawn): A method of preventing or treating hydro-mineral imbalance which comprises administering a patient in need thereof with a peptide according to claim 1, or a mimetic thereof, wherein said mimetic retains the binding specificity and/or physiological activity of said peptide and is obtained through a structural modification selected from the group consisting of:

replacement of one or more of the amino acids with unnatural amino acids,

conformational restraints,

isosteric replacement,

cyclization,

replacement of one or more amide bonds with non-amide bonds,

replacement of one or more amino acid side chains with a different chemical moiety,

protection of one or more of the N-terminus, the C-terminus, or one or more side chains with a protecting group, double bond, cyclization, or sterospecificity,

protection of the NH_2 and COOH hydrophilic groups by esterification with lipophilic alcohols by amidation and/or acetylation,

addition of a carboxylalkyl or aromatic hydrophobic chain at the NH_2 terminus,

retroinversion of the CO-NH amide bonds,

methylation of the amide functions, and

substitution of L-amino acids with D-amino acids.

Claim 28 (Withdrawn): The method of claim 27, for the prevention or treatment of bone, teeth, kidney, parathyroid, pancreas, intestine, stomach mucosa, prostate, and salivary gland disorders that are caused by hydro-mineral imbalance.

Claim 29 (Withdrawn): The method of claim 28, wherein the disorder is selected from the group consisting or hyper or hypo-parathyroidism, osteoporosis, pancreatitis, submandibular gland lithiasis, nephrolithiasis and osteodystrophy.

Claim 30 (Withdrawn): A method of preventing or treating impaired interpersonal and behavioural disorder which comprises administering a patient in need thereof with a peptide according to claim 1 or a mimetic thereof, wherein said mimetic retains the binding specificity and/or physiological activity of said peptide and is obtained through a structural modification selected from the group consisting of:

replacement of one or more of the amino acids with unnatural amino acids,

conformational restraints,

isosteric replacement,

cyclization,

replacement of one or more amide bonds with non-amide bonds,

replacement of one or more amino acid side chains with a different chemical moiety,

protection of one or more of the N-terminus, the C-terminus, or one or more side chains with a protecting group, double bond, cyclization, or sterospecificity,

protection of the NH_2 and COOH hydrophilic groups by esterification with lipophilic alcohols by amidation and/or acetylation,

addition of a carboxylalkyl or aromatic hydrophobic chain at the NH_2 terminus,

retroinversion of the CO-NH amide bonds,

methylation of the amide functions, and

substitution of L-amino acids with D-amino acids.

Claim 31 (Withdrawn): The method of claim 30, wherein the disorder is selected from the group consisting of avoidance disorder, decreased awareness disorder, autistic disorder, attention deficit hyperactivity disorder, hospitalism, impaired interpersonal functioning and relationship to the external world, schizoid personality disorder, schizophrenia, decreased interest in environment, impaired social activity linked to sexuality, and impaired sexual behaviour.

Claim 32 (Withdrawn): The method of claim 30, wherein the disorder is depressive disorder.

Claim 33 (Withdrawn): The method according to claim 22, for the prevention or treatment of inflammatory arthritis.

Claim 34 (Withdrawn): The method according to claim 22, wherein the peptide or derivative or mimetic thereof acts as a natriuretic agent.

Claim 35 (Withdrawn): The method according to claim 22, wherein the peptide or derivative or mimetic thereof acts as a diuretic agent.

Claim 36 (Withdrawn): The method according to claim 22, for the prevention or treatment of atherosclerosis.

Claim 37 (Withdrawn): The method according to claim 22, for the prevention or treatment of a tumor.

Claim 38 (Withdrawn): The method according to claim 22, for the prevention or treatment of inflammatory bowel disease.

Claim 39 (Withdrawn): The method according to claim 22, for the treatment of infections.

Claim 40 (Withdrawn): The method according to claim 22, for controlling immuno-inflammatory responses.

Claim 41 (Withdrawn): The method according to claim 22, for the treatment of a neurodegenerative disease.

Claim 42 (Withdrawn): The method according to claim 41, for the treatment of a neurodegenerative disease associated with amyloidosis.

Claim 43 (Withdrawn): A method of preventing or treating of a disease which comprises administering a patient in need thereof with a nucleic acid according to claim 10.

Claim 44 (Withdrawn): The method according to claim 43, wherein said nucleic acid from part of a vector.

Claim 45 (Withdrawn): A method of preventing or treating of a disease which comprises administering a patient in need thereof with an antibody according to claim 13.

Claim 46 (Withdrawn): A method of preventing or treating of a disease as defined in claim 22 which comprises administering a patient in need thereof with a BPLP protein.

Claim 47 (Withdrawn): A method of preventing or treating of a disease as defined in claim 22 which comprises administering a patient in need thereof with a nucleic acid that encodes a BPLP protein.

Claim 48 (Withdrawn): The method according to claim 47, wherein said nucleic acid form part of a vector.

Claim 49 (Withdrawn): A method of preventing or treating of a disease which comprises administering a patient in need thereof with an antibody directed against BPLP protein according to claim 14.

Claim 50 (Withdrawn): An *in vitro* method for prognosis, diagnosis or determination of the evolution of a condition involving an altered production of BPLP or of any of its maturation products, which method comprises detecting, or quantifying in a biological sample of a test subject, a BPLP protein or a maturation products thereof, and comparing the production of BPLP protein or maturation products with the production of the same in a biological sample of a control subject.

Claim 51 (Withdrawn): A method for a detection of the production of BPLP or of any of its maturation products is performed by contacting a biological sample with an antibody as defined in claim 13.

Claim 52 (Withdrawn): An *in vitro* method for prognosis or diagnosis of a condition involving an altered production of BPLP or of any of its maturation products, which method comprises detecting in a biological sample of a test subject, a quantitative and/or qualitative abnormality in the BPLP gene or in its transcript.

Claim 53 (Withdrawn): An *in vitro* method for screening compounds for their ability to bind to the NEP binding site for the BPLP protein or a maturation product thereof, comprising the steps of:

a) incubating a candidate compound with a NEP expressing cell, in the presence of the BPLP protein or a maturation product thereof, or in the presence of any peptide retaining the binding specificity or the physiological activity of BPLP protein or of its maturation products;

b) determining the ability of the candidate compound to compete with the BPLP protein or a maturation product thereof, or with the peptide retaining the binding specificity or the physiological activity of BPLP protein or of its maturation products, for binding to NEP.

Claim 54 (Withdrawn): The method of claim 53, comprising the steps of :

a) preparing a cell culture or preparing an organ specimen or a tissue sample containing NEP binding sites for the BPLP protein or maturation products thereof ;

b) adding the candidate compound to be tested in competition with half-saturation concentration of labeled BPLP protein or maturation product thereof, or any peptide that retains the binding specificity or the physiological activity of the BPLP protein or of its matured products ;

c) incubating the cell culture, organ specimen or tissue sample of step a) in the presence of the candidate compound during a time sufficient and under conditions for the specific binding to take place ;

d) quantifying the label specifically bound to the cell culture, organ specimen or tissue sample in the presence of various concentrations of candidate compound.

Claim 55 (Withdrawn): A method for determining the affinity of a compound that specifically binds to the NEP binding site for the BPLP protein or maturation products thereof, comprising the steps of :

a) preparing a cell culture or preparing an organ specimen or a tissue sample containing NEP binding sites for the BPLP protein or maturation products thereof ;

b) adding the candidate compound which has previously been labeled with a radioactive or a nonradioactive label ;

c) incubating the cell culture, organ specimen or tissue sample of step a) in the presence of the labeled candidate compound during a time sufficient and under conditions for the specific binding to take place ; and

d) quantifying the label specifically bound to the cell culture, organ specimen or tissue sample in the presence of various concentrations of the labeled candidate compound.

Claim 56 (Withdrawn): An *in vitro* method for screening compounds for their ability to act as agonists or antagonists of the BPLP protein or maturation products thereof on NEP activity, which method comprises the steps of :

a) incubating a candidate compound with a NEP expressing cell, in the presence of (i) the BPLP protein or a maturation product thereof, or any peptide retaining the binding specificity or the physiological activity of the BPLP protein or of its matured products, and (ii) a NEP substrate ;

b) determining the endoproteolysis of the NEP substrate by the NEP, wherein an increased endoproteolysis in the presence of the candidate compound, in comparison with the endoproteolysis in the absence of the candidate compound, is indicative of an antagonist activity; while a decreased endoproteolysis in the presence of the candidate compound, in

comparison with the endoproteolysis in the absence of the candidate compound, is indicative of an agonist activity.

Claim 57 (Withdrawn): The method of claim 56, for screening a compound that is an agonist of the BPLP protein or a maturation product thereof, comprising the steps of :

a) preparing a cell culture or preparing an organ specimen or a tissue sample containing NEP binding sites for the BPLP protein or a maturation product thereof;

b) incubating the cell culture, organ specimen or tissue sample of step a) at concentrations allowing measurement of NEP enzymatic activity in the presence of (i) the candidate compound, (ii) a half-saturating concentration of the BPLP protein or a maturation product thereof or any peptide retaining the binding specificity or the physiological activity of the BPLP protein or of its matured products and (iii) a NEP substrate, during a time sufficient for the endoproteolysis of the NEP substrate to take place under initial velocity conditions ;

c) quantifying the activity of the NEP present in the biological material of step a) by measuring the levels of NEP substrate endoproteolysis, respectively in the presence or in the absence of the candidate compound and in the presence or in the absence of the BPLP protein or a maturation product thereof, or of the peptide retaining the binding specificity or the physiological activity of the BPLP protein or of its matured products.

Claim 58 (Withdrawn): The method of claim 56 for screening a compound that is an antagonist of the BPLP protein or a maturation product thereof, comprising the steps of :

a) preparing a cell culture or preparing an organ specimen or a tissue sample containing NEP binding sites for the BPLP protein or a maturation product thereof;

b) incubating the cell culture, organ specimen or tissue sample of step a) at concentrations allowing measurement of NEP enzymatic activity under initial velocity conditions in the presence of a submaximal concentration of the BPLP protein or a maturation product thereof or any peptide retaining the binding specificity or the physiological activity of the BPLP protein or of its matured products, and a NEP substrate, in the presence of the candidate compound, during a time sufficient for the endoproteolysis of the NEP substrate to take place under initial velocity conditions ;

c) quantifying the activity of the NEP present in the biological material of step a) by measuring the levels of NEP substrate endoproteolysis, respectively in the presence or in the absence of the candidate compound and in the presence or in the absence of the BPLP protein or a maturation product thereof or of the peptide retaining the binding specificity or the physiological activity of the BPLP protein or of its matured products.

Claim 59 (Withdrawn): A molecular complex comprising :

- a metallo-ectopeptidase receptor, especially a NEP receptor or an APN receptor, binding site of the BPLP-protein or maturation products thereof ;

- the BPLP-protein or maturation products thereof.

Claim 60 (Withdrawn): A method of preventing or treating diseases wherein a modulation of the activity of said membrane metallopeptidase is sought which comprises administering a patient in need thereof with an agent that modulates the interaction between endogenous BPLP protein or maturation product and a membrane metallopeptidase.

Claim 61 (Withdrawn): A host cell comprising the vector of claim 11.

Claim 62 (Withdrawn): A pharmaceutical composition comprising the vector of claim 11.

Claim 63 (Withdrawn): A pharmaceutical composition comprising an antibody of claim 14.

Claim 64 (Withdrawn): A pharmaceutical composition of claim 18 comprising a second pharmaceutical agent that acts synergistically with BPLP-peptide.

Claim 65 (Canceled):

Claim 66 (Withdrawn): A method for a detection of the production of BPLP or of any of its maturation products is performed by contacting a biological sample with an antibody as defined in claim 14.

Claim 67 (Canceled):

SUPPORT FOR THE AMENDMENTS

Claims 2, 21, and 65 were previously canceled.

Claims 4, 20, and 67 are canceled herein.

Claims 1, 6, 15, and 16 have been amended.

The amendment to Claims 1, 6, 15, and 16 is supported by the specification, for example, at pages 7-10 and original and previously pending Claims 1, 4, 6, 15, and 16.

No new matter has been added by the present amendments.